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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/815,557	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-53 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-53 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The application fails to follow the standards or format for U.S. applications. Claims 14 and 53 will not be given further consideration. In the instant case, the language set forth in the claims is such that the precise nature of Applicant's invention is incomprehensible, and thus unsearchable by the Examiner. It is suggested that the claim language be corrected so as to place the application in better form for examination.

Claim 53 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim since the claimed method encompasses claim 33 ***or 35 to 36*** [emphasis added]. The claim does not refer to claims 35 and 36 in the alternative. See MPEP § 608.01(n). Accordingly, the claim had not been further treated on the merits. It is suggested that the claim language be corrected so as to place the application in better form for examination.

See MPEP 608.01(n)

B. Unacceptable Multiple Dependent Claim Wording

1. Claim Does Not Refer Back in the Alternative Only

Claim 10. A gadget as in claims 1-3 or 7-9, in which ---

It is also noted that numerous claims recite the generic term "agent" in several, non-identical contexts. The Examiner has established the following Requirement for Restriction based upon the Examiner's interpretation of the generic term "agent" and the corresponding context in the claim set. If the Examiner's interpretation is not the same as Applicant's, then Applicant is strongly encouraged to be more explicit in reference to each "agent" to be selected, used for contacting, identified, etc...

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I, claims 1-13 and 15-32, drawn to a method of identifying one or more agents with therapeutic activity to treat one or more symptoms of a disease which is associate with aberrant expression or activity of epithelial sodium channels (ENaC), classified in class 514, subclass 44.

Group II, claims 33-52, drawn to a method of treating a condition associated with increased epithelial sodium channel levels or activity in a mammal at risk of or having the condition comprising administering to the mammal one or more agents and a gene therapy vector, classified in class 514, subclass 44.

Inventions I and II are directed to related processes. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the Groups I method to identify compounds that will be effective in treating a disease or disorder, may be performed *ex vivo* or *in vivo* and does not require the cells to be of diseased origin; whereas, Group II is a method of treatment of a mammal having or at risk of having a condition associated, and thus requires *in vivo* administration. Furthermore, the purpose of Group I is to discover and identify useful compounds; which is a distinctly different purpose and yields a distinctly different result than the Group II method of treating a mammal having or at risk of having a particular disease.

A search for a method of identifying one or more therapeutic agents would not be co-extensive with a search for a method of treating a condition. Further, a reference rendering a method of identifying one or more therapeutic agents as anticipated or obvious over the prior art would not necessarily also render a method of treating a condition as anticipated or obvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

2. **Should Applicant elect Invention I, further group restriction is required under 35 U.S.C. 121.**

Group IA, claims 1-2, 5-9, 13, 15-23 and 28-32, drawn to a method of identifying an agent with dual therapeutic activity in mammalian cells, classified in class 514, subclass 44.

Group IB, claims 10-32, drawn to a method of identifying an agent that decreases the level or amount of transcription of one or more subunits of epithelial sodium channels (ENaC) in mammalian cells, classified in class 514, subclass 1.

Invention I, Groups IA and IB are related as distinct processes. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, The Group IA method to identify agents requires the use of a gene therapy vector; whereas, the Group IB method to identify agents does not require the use of any gene delivery vehicle or gene therapy vector. Rather, the specific biological effect sought in the Group IB method is a decrease in transcription of the genes encoding one or more subunits of ENaC. Furthermore, the invention of Group IA is a method of identifying an agent with dual therapeutic activity; whereas, no such dual activity is required of the agent in Group IB that is capable of decreasing the transcription of an ENaC subunit(s).

A search for a method of identifying an agent with dual therapeutic activity in the context of a gene therapy vector would not be co-extensive with a search a method of identifying an agent that decreases the level or amount of transcription of one or more subunits of ENaC. Further, a reference rendering an agent that specifically decreases the transcription of a gene as anticipated or obvious over the prior art would not necessarily also render an agent that generally enhances the efficacy of a gene therapy vector as anticipated or obvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does

not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed inventive method subgroup, even though this requirement is traversed. Failure to elect an inventive method subgroup from Invention IA or IB above consonant with Applicant's elected Invention I, may result in a notice of non-responsive amendment.

Should Applicant elect Invention II, a further group restriction is required under 35 U.S.C. 121.

Group IIA, claims 33 and 37-52, drawn to a method of treating a condition associated with increased epithelial sodium channel levels or activity, the method comprising contacting a mammal with an agent that inhibits or decreases transcription and enhances the efficacy of gene therapy vectors, classified in class 514, subclass 44.

Group IIB, claims 34 and 37-52, drawn to a method of treating a condition associated with increased epithelial sodium channel levels or activity, the method comprising contacting a mammal with an agent that inhibits or decreases transcription, wherein the agent is not a gene or gene product, and wherein the agent is a proteasome modulating agent, classified in class 514, subclass 44.

Group IIC, claims 35 and 37-52, drawn to a method of treating a condition associated with increased epithelial sodium channel levels or activity, the method comprising contacting a mammal with an agent that inhibits or decreases transcription, classified in class 514, subclass 44.

Group IID, claims 36-52, drawn to a method of treating a condition associated with creased epithelial sodium channel levels or activity, the method comprising contacting a

mammal with an agent that inhibits or decreases transcription and enhances transduction of viruses that infect mammalian cells, classified in class 514, subclass 44.

Invention II, Groups IIA-IID are related as distinct processes. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, each method is of distinctly different design, mode of operation and effect and is mutually exclusive of the other methods. For example, the Group IIA method uses an agent that enhances the efficiency of a gene therapy vector; whereas, the Group IIB method uses a proteasome modulating agent and the Group IID method uses an agent that enhances transduction of an enormous genus of viruses capable of infecting an enormous genus of mammalian cells. Thus, one of ordinary skill in the art would recognize that the functional properties of the recited agents in the Group IIA-IID methods are non-obvious variants. Each agent functionality confers a unique, distinctly different effect on the cell which it contacts that are not obvious variations of each other because the ability to inhibit or decrease the transcription of one or more ENaC subunit genes directly, as compared to the ability to alter the level, amount or activity of a tertiary molecule, e.g. transcription factor, are the direct result of the given agent's structure and one of ordinary skill in the art cannot predict *a priori* which structure will affect only the transcription of an ENaC subunit gene, which structure will affect only a tertiary molecule that is capable of altering the transcription of an ENaC subunit gene, and which structure is capable of affecting both the transcription of an ENaC subunit gene and a tertiary molecule that is capable of altering the transcription of an ENaC subunit gene and modulate the proteosome or enhance viral transduction. The biological activity of the agent(s) is directly dependent on the structure of the composition, and thus is mutually exclusive of the other agents.

A search for a method using a selected agent that enhances viral transduction in mammalian cells would not be co-extensive with a search for a method using a selected agent that modulates the proteasome. Further, a reference rendering a method using an agent that inhibits or decreases transcription of one ENaC subunit gene as anticipated or obvious over the

prior art would not necessarily also render a method using an agent that alters the level, amount or activity of a molecule that is capable of affecting transcription of one or more ENaC subunit genes, e.g. a transcription factor, as anticipated or obvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another species, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed inventive method subgroup, even though this requirement is traversed. Failure to elect an inventive method subgroup from Invention IIA-IID above consonant with Applicant's elected Invention II, may result in a notice of non-responsive amendment.

3. **Should Applicant elect any of Inventions IA-IB or Inventions IIA-IID, a species election is required under 35 U.S.C. 121.** Claims 16-19 and 38-41 recite patentably distinct **physiological agent categories** associated with an agent that prohibit proper examination of these claims. Therefore, election is required under 35 U.S.C. 121 of any of Inventions IA-IB or Inventions IIA-IID and one **physiological agent category** (i)-(iv) consonant with Applicant's elected invention for prosecution on the merits to which the claims shall be restricted, wherein the **physiological agent category**, specifically:

i) is an antibiotic, as recited in Claims 16 and 39,

ii) is a chemotherapeutic, as recited in Claims 17 and 38,

iii) is a lipid lowering compound, as recited in Claims 18 and 41, or

iv) is a food additive, as recited in Claims 19 and 40.

Each physiological agent category confers a unique, distinctly different effect on the cell which it contacts that are not obvious variations of each other because one skilled in the art does not expect food additives such as alpha tocopherol to have the same chemical and physiological properties to effect the inhibition or treatment of one or more symptoms of a disease associated with aberrant expression or activity of epithelial sodium channels as chemotherapeutics such as

suramin or 5-fluorouracil, for example. The cell biological processes described in these inventive functional groups are distinctly different. One of ordinary skill in the art could readily consult any cell biology reference textbook (e.g., Molecular Biology of the Cell, Alberts et al., Garland Publishing) describing the structure, characteristics and biological properties for each of the cell biological processes to be affected by a given agent, and would appreciate that based on such reference disclosures alone or in combination, that these agent functionalities are distinct and separate.

A search for a food additive would not be co-extensive with a search for an antibiotic. Further, a reference rendering a chemotherapeutic as anticipated or obvious over the prior art would not necessarily also render a lipid-lowering compound as anticipated or obvious over the prior art. Similarly, a finding that a food additive was novel and unobvious over the prior art would not necessarily extend to a finding that a chemotherapeutic was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a disclosed **physiological agent category** species, even though this requirement is traversed. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Failure to elect a physiological agent category species consonant with Applicant's elected Inventions IA-IB or Inventions IIA-IID may result in a notice of non-responsive amendment.

Should Applicant elect any of Inventions IA-IB or Inventions IIA-IID and a physiological agent category from (i)-(iv) from above, a further species election is required under 35 U.S.C. 121. Claims 20 and 37 recite a plurality of disclosed patentably distinct **physiological agent compounds** of distinctly different biological functionality. Therefore,

election is required under 35 U.S.C. 121 of any of Inventions IA-IB or Inventions IIA-IID and a **physiological agent category** from (i)-(iv) and one **physiological agent compound** from the list consisting of the **physiological agent compounds** recited in Claim 20 (Inventions IA-IB) or Claim 37 (Inventions IIA-IID) consonant with Applicant's elected invention for prosecution on the merits to which the claims shall be restricted.

Each agent possesses an independent and distinctly different structure and confers a unique, distinctly different effect on the cell which it contacts that are not obvious variations of each other because one skilled in the art does not expect food additives such as tannic acid to have the same chemical properties as chemotherapeutics such as cisplatin, for example.

A search for doxorubicin would not be co-extensive with a search for tannic acid. Further, a reference rendering cisplatin as anticipated or obvious over the prior art would not necessarily also render simvastatin as anticipated or obvious over the prior art. Similarly, a finding that epoxomicin was novel and unobvious over the prior art would not necessarily extend to a finding that camptothecin was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another species, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed **physiological agent compound**, even though this requirement is traversed. Failure to elect a **physiological agent compound** consonant with Applicant's elected Inventions IA-IB or Inventions IIA-IID and a **physiological agent category** from (i)-(iv) from above, may result in a notice of non-responsive amendment.

Should Applicant elect any of Inventions IA-IB or Inventions IIA-IID and a physiological agent category from (i)-(iv) and a physiological agent compound from above, a further species election is required under 35 U.S.C. 121. Claims recite, a plurality of disclosed patentably distinct **cellular functionalities** associated with an agent that is to be identified. Therefore, election is required of one of Inventions IA-IB or Inventions IIA-IID and **a**

physiological agent category from (i)-(iv) and a **physiological agent compound** and one **agent cellular functionality** from (v)-(xiii) below, wherein the agent, specifically:

v) modulates subcellular localization of proteasomes, as recited in Claims 21 and 46,

vi) does not alter post-translational processing of an ENaC, as recited in Claims 22 and 42,

vii) modulates transcription of a molecule that regulates ENaC transcription, as recited in Claims 23 and 44,

viii) decreases the level of transcription, as recited in Claim 24-27,

ix) modulates transport of molecules to or from the nucleus, as recited in Claims 28 and 45,

x) is an endosomal protease inhibitor, as recited in Claim 29,

xi) is a cysteine protease inhibitor, as recited in Claim 30,

xii) is not TPA, as recited in Claims 31 and 43, or

xiii) alters endosomal processing, as recited in Claim 32.

The cell biological processes described in these inventive functional groups are distinctly different. One of ordinary skill in the art could readily consult any cell biology reference textbook (e.g., Molecular Biology of the Cell, Alberts et al., Garland Publishing) describing the structure, characteristics and biological properties for each of the cell biological processes to be affected by a given agent, and would appreciate that based on such reference disclosures alone or in combination, that these agent functionalities are distinct and separate.

A search for a cysteine protease inhibitor would not be co-extensive with a search for an agent that alters endosomal processing. Further, a reference rendering transcriptional modulation as anticipated or obvious over the prior art would not necessarily also render enhanced viral transduction as anticipated or obvious over the prior art. Similarly, a finding that an agent that modulates transport of molecules to or from the nucleus was novel and unobvious over the prior art would not necessarily extend to a finding that an agent that is not TPA was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly

burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect one disclosed **agent cellular functionality**, even though this requirement is traversed. Failure to elect an **agent cellular functionality** from (v)-(xiii) above consonant with Applicant's elected Inventions IA-IB or Inventions IIA-IID and **a physiological agent category** from (i)-(iv) and a **physiological agent compound** from above, may result in a notice of non-responsive amendment.

Should Applicant elect any of Inventions IA-IB or Inventions IIA-IID and a physiological agent category from (i)-(iv) and a physiological agent compound and an agent cellular functionality from (v)-(xiii) above, a further species election is required under 35 USC 121. Currently, Claim 4 and Claim 52 of this application recite a plurality of disclosed patentably distinct virus species that prohibit proper examination of these claims. Therefore, election is required under 35 U.S.C. 121 of one of Inventions IA-IB or Inventions IIA-IID and a **physiological agent category** from (i)-(iv) and a **physiological agent compound** and an **agent cellular functionality** from (v)-(xiii) and one **virus type** from (xiv)-(xvii) below, regarding a patently distinct viruses consonant with Applicant's elected invention for prosecution on the merits to which the claims shall be restricted if no generic claim (specifically, Claim 3 for Inventions IA-IB, Claim 33 for Invention IIA, and Claim 36 for Invention IID) is finally held to be allowable wherein the virus is, specifically:

xiv) lentiviral,

xv) retroviral,

xvi) adenoviral, or

xvii) adeno-associated viral.

Each virus type has a distinctly different structure, is mutually exclusive of the other viruses and yields distinctly different effect. For example, the cellular tropism, means of cell entry and replication within the host cell are distinctly different for each virus type. In contrast to

retroviruses, adenoviruses do not integrate their genetic material into the host genome, thus preventing the risk of insertion mutagenesis. Thus, each virus yields distinctly different effects.

A search for a retrovirus would not be co-extensive with a search for an adeno-associated virus Further, a reference rendering a lentivirus as anticipated or obvious over the prior art would not necessarily also render an adenovirus as anticipated or obvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another species, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed **virus type** species, even though this requirement is traversed. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Failure to elect a **virus type** species consonant with Applicant's elected Inventions IA-IB or Inventions IIA-IID and a **physiological agent category** from (i)-(iv) and a **physiological agent compound** and an **agent cellular functionality** from (v)-(xiii), may result in a notice of non-responsive amendment.

Should Applicant elect Invention IA or any of Inventions IIA-IID and a physiological agent category from (i)-(iv) and a physiological agent compound and an agent cellular functionality from (v)-(xiii) and a virus type from (xiv)-(xvii) from above, a further species election is required under 35 USC 121. Currently, Claim 2 of this application is generic to, and Claims 33-36 recite a plurality of, **selected transcriptional agent activities** that prohibit proper examination of the claims. Therefore, election is required under 35 U.S.C. 121 of Invention IA or any of Inventions IIA-IID and a **physiological agent category** from (i)-(iv) and **physiological agent compound** and an **agent cellular functionality** from (v)-(xiii) and a **virus type** from (xiv)-(xvii) above and one **selected transcriptional agent activity** from (xviii)-(xxxi)

below consonant with Applicant's elected invention for prosecution on the merits to which the claims shall be restricted, specifically:

xviii) the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 7,

xix) the selected agent is effective to decrease the level or amount of transcription of the α, β and γ subunits of ENaC, as recited in Claim 8,

xx) the selected agent is effective to alter ENaC activity, as recited in Claim 9,

xxi) the selected agent enhances the efficiency of gene therapy vectors and is effective to decrease the level or amount of transcription of one or more subunits of ENaC and alters the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes, as recited in Claim 33,

xxii) the selected agent enhances the efficiency of gene therapy vectors and is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 33,

xxiii) the selected agent enhances the efficiency of gene therapy vectors and is effective to alter the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes, as recited in Claim 33,

xxiv) the selected proteasome modulating agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 34,

xxv) the selected proteasome modulating agent is effective to alter the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes, as recited in Claim 34,

xxvi) the selected proteasome modulating agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and alter the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes, as recited in Claim 34,

xxvii) the selected agent is effective to decrease the level or amount of transcription of the α, β and γ subunits of ENaC, as recited in Claim 35,

xxviii) the selected agent is effective to alter the level, amount or activity of a molecule that alters transcription of the α, β and γ subunits of ENaC, as recited in Claim 35,

xxix) the selected agent enhances transduction of viruses which infect mammalian cells and is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 36,

xxx) the selected agent enhances transduction of viruses which infect mammalian cells and is effective to alter the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes, as recited in Claim 36, or

xxxi) the selected agent enhances transduction of viruses which infect mammalian cells and is effective to decrease the level or amount of transcription of one or more subunits of ENaC and is effective to alter the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes, as recited in Claim 36.

In the instant case, each agent functionality species confers a unique, distinctly different effect on the cell which it contacts that are not obvious variations of each other because the ability to inhibit or decrease the transcription of one or more ENaC subunit genes directly, as compared to the ability to alter the level, amount or activity of a tertiary molecule, are the direct result of the given agent's structure and one of ordinary skill in the art cannot predict *a priori*

which structure will affect only the transcription of an ENaC subunit gene, which structure will affect only a tertiary molecule that is capable of altering the transcription of an ENaC subunit gene, and which structure is capable of affecting both the transcription of an ENaC subunit gene and a tertiary molecule that is capable of altering the transcription of an ENaC subunit gene. The biological activity of the agent is directly dependent on the structure of the composition, and thus is mutually exclusive of the other agents. An agent that alters the activity of ENaC may act at the post-transcriptional level and affect the post-translational processing of an ENaC subunit or the holoreceptor without affecting the transcription of the ENaC subunits, and thus is structurally distinct from both the agent that specifically decreases the expression of one specific subunit of the ENaC holoreceptor as well as the agent that decreases the expression of the α, β and γ subunits of ENaC. Furthermore, Claims 33-36 recite an agent that has multiple, distinctly different biological properties that are non-obvious variations of an agent that possesses only one recited property.

A search for a selected agent that decreases the enzymatic activity of the ENaC holoreceptor would not be co-extensive with a search for a selected agent that decreases the level of transcription of the a subunit, and a search for an agent that inhibits or decreases transcription of one or more ENaC subunit genes would not be co-extensive with a search for an agent that alters the level, amount or activity of a molecule that is capable of affecting transcription of one or more ENaC subunit genes. Further, a reference rendering a selected agent that decreases the level of transcription of the α subunit as anticipated or obvious over the prior art would not necessarily also render a selected agent that decreases the enzymatic activity of the ENaC holoreceptor as anticipated or obvious over the prior art, and a reference rendering an agent that inhibits or decreases transcription of one or more ENaC subunit genes as anticipated or obvious over the prior art would not necessarily also render an agent that inhibits or decreases transcription of one or more ENaC subunit genes and alters the level, amount or activity of a molecule that alters transcription of one or more ENaC subunit genes as anticipated or obvious over the prior art. Similarly, a finding that a selected agent is effective to decrease the level or amount of transcription of the α, β and γ subunits of ENaC was novel and unobvious over the prior art would not necessarily extend to a finding that a selected agent is effective to decrease

the level or amount of transcription of one subunit of ENaC was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another species, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed **selected transcriptional agent activity**, even though this requirement is traversed. Applicant is advised that a reply to this requirement must include an identification of the **selected transcriptional agent activity** species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Failure to elect a **selected transcriptional agent activity** from (xviii)-(xxxi) above consonant with Applicant's elected Invention IA or any of Inventions IIA-IID and a **physiological agent category** from (i)-(iv) and **physiological agent compound** and an **agent cellular functionality** from (v)-(xiii) and a **virus type** from (xiv)-(xvii) above, may result in a notice of non-responsive amendment.

Should Applicant elect any of Inventions IA-IB and a physiological agent category from (i)-(iv) and physiological agent compound and an agent cellular functionality from (v)-(xiii) and a virus type from (xiv)-(xvii) and a selected transcriptional agent activity from (xviii)-(xxxi) above (as required of Invention IA), a further species election is required under 35 USC 121. Currently, Claim 15 of this application recites a plurality of disclosed patentably distinct **mammalian cell type** species that prohibit proper examination of this claim. Therefore, election is required under 35 U.S.C. 121 of any of Inventions IA-IB and a **physiological agent category** from (i)-(iv) and **physiological agent compound** and an **agent cellular functionality** from (v)-(xiii) and a **virus type** from (xiv)-(xvii) and a **selected transcriptional agent activity** from (xviii)-(xxxi) and one **mammalian cell type** species from the list consisting of the mammalian cells recited in Claim 15 consonant with Applicant's elected invention for prosecution on the merits to which the claims shall be restricted.

In the instant case, the mammalian cells are distinctly different because an agent which is capable of decreasing transcription of an ENaC subunit, e.g. an antisense oligonucleotide, in a rabbit cell may not function in a human cell given the genetic differences in the genomic sequence. Furthermore, the genetic redundancy of sodium channels encoded in the diverse mammalian genomes may obscure the identification of an agent that is functional in human cells but not murine cells.

A search for human cells would not be co-extensive with a search for rabbit cells. Further, a reference rendering murine cells as anticipated or obvious over the prior art would not necessarily also render canine cells as anticipated or obvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another species, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed **mammalian cell type** species, even though this requirement is traversed. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Failure to elect a **mammalian cell type** species consonant with Applicant's elected Inventions IA-IB and a **physiological agent category** from (i)-(iv) and **physiological agent compound** and an **agent cellular functionality** from (v)-(xiii) and a **virus type** from (xiv)-(xvii) and a **selected transcriptional agent activity** from (xviii)-(xxxi) (as required of Invention IA), may result in a notice of non-responsive amendment.

Should Applicant traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER